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FILE 'HOME' ENTERED AT 08:31:48 ON 01 OCT 2007

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FILE 'MEDLINE' ENTERED AT 08:32:12 ON 01 OCT 2007

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=> s (traumatic(w)brain(w)injury or TBI) and stroke and mechanism
L1          317 (TRAUMATIC(W) BRAIN(W) INJURY OR TBI) AND STROKE AND MECHANISM

=> s l1 py<2002
MISSING OPERATOR L1 PY<2002
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l1 and py<2002
   2 FILES SEARCHED...
L2           96 L1 AND PY<2002

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           42 DUP REM L2 (54 DUPLICATES REMOVED)

=> dis his

     (FILE 'HOME' ENTERED AT 08:31:48 ON 01 OCT 2007)

     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 08:32:12 ON 01 OCT 2007
L1           317 S (TRAUMATIC(W)BRAIN(W)INJURY OR TBI) AND STROKE AND MECHANISM
L2            96 S L1 AND PY<2002
L3            42 DUP REM L2 (54 DUPLICATES REMOVED)

=> dis ibib abs l3 1-10

L3   ANSWER 1 OF 42  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
ACCESSION NUMBER:    2001:485112  BIOSIS
DOCUMENT NUMBER:     PREV200100485112
TITLE:               Mechanisms of neuronal apoptosis and
                     excitotoxicity.
AUTHOR(S):           Mattson, Mark P. [Reprint author]
CORPORATE SOURCE:    Laboratory of Neurosciences, National Institute on Aging,
                     Baltimore, MD, USA
SOURCE:              Mattson, Mark P. (2001) pp. 1-20. Contemporary
                     Neuroscience. Pathogenesis of neurodegenerative disorders.
                     print.
                     Publisher: Humana Press Inc., 999 Riverview Drive, Suite
                     208, Totowa, NJ, 07512, USA.
                     ISBN: 0-89603-838-6 (cloth).
DOCUMENT TYPE:       Book
                     Book; (Book Chapter)
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NEWS 2	JUL 02	LMEDLINE coverage updated
NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	BEILSTEIN updated with new compounds
NEWS 12	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 13	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 14	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 15	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 16	AUG 27	USPATOLD now available on STN
NEWS 17	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 19	SEP 13	FORIS renamed to SOFIS
NEWS 20	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 21	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 22	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 23	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 2001
Last Updated on STN: 23 Feb 2002

L3 ANSWER 2 OF 42 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001340690 EMBASE
TITLE: Effects of matrix metalloproteinase-9 gene knock-out on the proteolysis of blood-brain barrier and white matter components after cerebral ischemia.
AUTHOR: Asahi M.; Wang X.; Mori T.; Sumii T.; Jung J.-C.; Moskowitz M.A.; Fini M.E.; Lo E.H.
CORPORATE SOURCE: Dr. E.H. Lo, Neuroprotection Research Laboratory, Department of Neurology, Harvard Medical School, Massachusetts Gen. Hosp. E. 149-2322, Charlestown, MA 02129, United States. Lo@helix.mgh.harvard.edu
SOURCE: Journal of Neuroscience, (1 Oct 2001) Vol. 21, No. 19, pp. 7724-7732.
Refs: 55
ISSN: 0270-6474 CODEN: JNRSDS
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 18 Oct 2001
Last Updated on STN: 18 Oct 2001

AB Deleterious processes of extracellular proteolysis may contribute to the progression of tissue damage after acute brain injury. We recently showed that matrix metalloproteinase-9 (MMP-9) knock-out mice were protected against ischemic and traumatic brain injury.
In this study, we examined the mechanisms involved by focusing on relevant MMP-9 substrates in blood-brain barrier, matrix, and white matter. MMP-9 knock-out and wild-type mice were subjected to transient focal ischemia. MMP-9 levels increased after ischemia in wild-type brain, with expression primarily present in vascular endothelium. Western blots showed that the blood-brain barrier-associated protein and MMP-9 substrate zonae occludens-1 was degraded after ischemia, but this was reduced in knock-out mice. There were no detectable changes in another blood-brain barrier-associated protein, occludin. Correspondingly, blood-brain barrier disruption assessed via Evans Blue leakage was significantly attenuated in MMP-9 knock-out mice compared with wild types. In white matter, ischemic degradation of the MMP-9 substrate myelin basic protein was significantly reduced in knock-out mice compared with wild types, whereas there was no degradation of other myelin proteins that are not MMP substrates (proteolipid protein and DM20). There were no detectable changes in the ubiquitous structural protein actin or the extracellular matrix protein laminin. Finally, 24 hr lesion volumes were significantly reduced in knock-out mice compared with wild types. These data demonstrate that the protective effects of MMP-9 gene knock-out after transient focal ischemia may be mediated by reduced proteolytic degradation of critical blood-brain barrier and white matter components.

L3 ANSWER 3 OF 42 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001327583 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11395392
TITLE: Hibernation, a model of neuroprotection.
AUTHOR: Zhou F; Zhu X; Castellani R J; Stimmelmayr R; Perry G; Smith M A; Drew K L
CORPORATE SOURCE: Institute of Arctic Biology and Department of Chemistry and Biochemistry, University of Alaska Fairbanks, 99775, USA.
CONTRACT NUMBER: NS38648 (NINDS)
NS41069 (NINDS)

SOURCE: The American journal of pathology, (2001 Jun)
Vol. 158, No. 6, pp. 2145-51.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 9 Jul 2001
Last Updated on STN: 9 Jul 2001
Entered Medline: 5 Jul 2001

AB Hibernation, a natural model of tolerance to cerebral ischemia, represents a state of pronounced fluctuation in cerebral blood flow where no brain damage occurs. Numerous neuroprotective aspects may contribute in concert to such tolerance. The purpose of this study was to determine whether hibernating brain tissue is tolerant to penetrating brain injury modeled by insertion of microdialysis probes. Guide cannulae were surgically implanted in striatum of Arctic ground squirrels before any of the animals began to hibernate. Microdialysis probes were then inserted in some animals after they entered hibernation and in others while they remained euthermic. The brain tissue from hibernating and euthermic animals was examined 3 days after implantation of microdialysis probes. Tissue response, indicated by examination of hematoxylin and eosin-stained tissue sections and immunocytochemical identification of activated microglia, astrocytes, and hemeoxygenase-1 immunoreactivity, was dramatically attenuated around probe tracks in hibernating animals compared to euthermic controls. No difference in tissue response around guide cannulae was observed between groups. Further study of the mechanisms underlying neuroprotective aspects of hibernation may lead to novel therapeutic strategies for stroke and traumatic brain injury.

L3 ANSWER 4 OF 42 EMBASE
ACCESSION NUMBER: 2001136278 EMBASE
TITLE: Neuroprotective agents in traumatic brain injury.
AUTHOR: Maas A.I.R.
CORPORATE SOURCE: Dr. A.I.R. Maas, Erasmus Univ. Medical Ctr. Rotterdam, Department of Neurosurgery, Dr. Molewaterplein 40, 3015 GD Rotterdam, Netherlands. maas@neur.azr.nl
SOURCE: Expert Opinion on Investigational Drugs, (2001) Vol. 10, No. 4, pp. 753-767.
Refs: 99
ISSN: 1354-3784 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Apr 2001
Last Updated on STN: 30 Apr 2001

AB The role of neuroprotection in traumatic brain injury (TBI) is reviewed. Basic research and experimental investigations have identified many different compounds with potential neuroprotective effect. However, none of the Phase III trials performed in TBI have been successful in convincingly demonstrating efficacy in the overall population. A common misconception

is that consequently these agents are ineffective. The negative results as reported in the overall population may in part be caused by specific aspects of the head injury population as well as by aspects of clinical trial design and analysis. The heterogeneity of the TBI population causes specific problems, such as a risk of imbalances between placebo and treated groups but also causes problems when a possible treatment effect is evaluated in relation to the prognostic effect present. Trials of neuroprotective agents should be targeted first of all to a population in which the mechanism at which the agent is directed is likely to be present and secondly to a population in which the chances of demonstrating efficacy are realistic, e.g., to patients with an intermediate prognosis. The possibilities for concomitant or sequential administration of different neuroprotective agents at different times deserve consideration. The potential for neuroprotection in TBI remains high and we should not be discouraged by recent failures obtained up until now. Rather, prior to initiating new trials, careful consideration of experimental evidence is required in order to optimise chances for mechanistic targeting and lessons learned from previous experience need to be taken to heart in the design of future studies.

L3 ANSWER 5 OF 42 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001229737 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11295994
TITLE: Multiple simultaneous intracerebral hemorrhages: clinical features and outcome.
AUTHOR: Maurino J; Saposnik G; Lepera S; Rey R C; Sica R E
CORPORATE SOURCE: Department of Neurology, Hospital J. M. Ramos Mejia, Soler 4019, Sexto Piso, Buenos Aires 1425, Argentina.. jorgemaurino@hotmail.com
SOURCE: Archives of neurology, (2001 Apr) Vol. 58, No. 4, pp. 629-32.
Journal code: 0372436. ISSN: 0003-9942.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 2 May 2001
Last Updated on STN: 25 Jan 2002
Entered Medline: 26 Apr 2001

AB BACKGROUND: The simultaneous occurrence of intracerebral hemorrhages in different arterial territories is an uncommon clinical event. Its predisposing factors and pathophysiological mechanisms are not clearly defined. OBJECTIVE: To analyze the frequency, risk factors, clinical features, neuroimaging findings, and outcome of multiple simultaneous intracerebral hemorrhages (SIHs). PATIENTS AND METHODS: We studied all patients with acute stroke admitted to our hospital from July 18, 1997, through December 18, 1999. Multiple SIHs were defined as the presence of 2 or more intracerebral hemorrhages affecting different arterial territories with identical computed tomographic density profiles. Patients with a history of traumatic brain injury were excluded from this study. Diagnostic investigation included routine blood and urine tests, coagulation studies, a chest radiograph, electrocardiogram, 2-dimensional transthoracic echocardiography, and computed tomography of the head without contrast medium. Disability was assessed using the National Institutes of Health Stroke Scale and Modified Rankin Scale. RESULTS: Among 142 patients with hemorrhagic stroke, we found 4 (2.8%) with SIHs. All 4 patients had a history of uncontrolled arterial hypertension. We excluded other potential causes of multiple SIHs by using appropriate diagnostic tests. The most common clinical manifestations were headache and weakness. Localization of hematomas was supratentorial, except for one patient who had both infratentorial and supratentorial hemorrhages. The mean National Institutes of Health score on admission was 15 and the

Modified Rankin Scale score was higher than 4 at 3 months. CONCLUSIONS: In our study, all patients with multiple SIHs had arterial hypertension and a poor outcome. Additional analytic studies, including new imaging techniques, can help to elucidate the association between arterial hypertension and multiple SIHs, risk factors, and underlying mechanisms of this clinical condition.

L3 ANSWER 6 OF 42 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:508992 BIOSIS
DOCUMENT NUMBER: PREV200100508992
TITLE: Gene expression following rat forebrain ischemia by microarray assay and immunocytochemistry.
AUTHOR(S): Michael, D. B. [Reprint author]; Rafols, J. A. [Reprint author]; Petrov, T. [Reprint author]; Guyot, L. L. [Reprint author]; Irwin, L. N.
CORPORATE SOURCE: Neurological Surgery and Anatomy and Cell Biol., Wayne State University School of Medicine, Detroit, MI, USA
SOURCE: Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 572. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Oct 2001
Last Updated on STN: 23 Feb 2002

AB Ischemic secondary injury mechanisms complicate stroke and traumatic brain injury (TBI). We tested the hypothesis that gene expression following ischemia can be characterized using microarray assay (ma) combined with immunocytochemistry (ic). Methods: Pulsinelli forebrain 20 minute ischemic and sham operated control rat brains were dissected and adjacent regions were subjected to ma (Research Genetics) or ic for Endothelin receptors A and B (ET-A and ET-B). Experimental and control cDNA membranes were compared using PathwaysTM 3 software. An arbitrary criterion of 25% change from control was used to report up or down regulation. Results: We found 4.6% upregulated and 1.3% downregulated genes out of the 5000 gene transcripts analyzed in the hippocampus. Up regulated genes included Kid-1, TCP-1 and apolipoprotein E. Actin gamma 2 was downregulated. ET-B was unchanged. ET-A was localized by ic in the mossy fiber zone of CA1 and the dentate gyrus of the hippocampus in controls and experimentals. ET-B was localized in neurons and astrocytes in all hippocampal regions. Semiquantitative analysis revealed a reduction by apprx50% of the ic reaction intensity for ET-A and an increase by apprx30% for ET-B after ischemia. Discussion: These results demonstrate differential gene expression after ischemia by both ma and ic. Further study will provide new insight into the pathophysiology and treatment of stroke and TBI.

L3 ANSWER 7 OF 42 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001479027 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11522441
TITLE: Neuroprotective adaptations in hibernation: therapeutic implications for ischemia-reperfusion, traumatic brain injury and neurodegenerative diseases.
AUTHOR: Drew K L; Rice M E; Kuhn T B; Smith M A
CORPORATE SOURCE: Institute of Arctic Biology, University of Alaska Fairbanks, Fairbanks, AK 99775-7000, USA.. ffkld@uaf.edu
CONTRACT NUMBER: NS-34115 (NINDS)
NS38648 (NINDS)
NS41069-01 (NINDS)

SOURCE: Free radical biology & medicine, (2001 Sep 1)
Vol. 31, No. 5, pp. 563-73. Ref: 151
Journal code: 8709159. ISSN: 0891-5849.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 28 Aug 2001
Last Updated on STN: 22 Jan 2002
Entered Medline: 14 Dec 2001

AB Brains of hibernating mammals are protected against a variety of insults that are detrimental to humans and other nonhibernating species. Such protection is associated with a number of physiological adaptations including hypothermia, increased antioxidant defense, metabolic arrest, leukocytopenia, immunosuppression, and hypocoagulation. It is intriguing that similar manipulations provide considerable protection as experimental treatments for central nervous system injury. This review focuses on neuroprotective mechanisms employed during hibernation that may offer novel approaches in the treatment of stroke, traumatic brain injury, and neurodegenerative diseases in humans.

L3 ANSWER 8 OF 42 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001347914 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11410269
TITLE: Brain damage, sex hormones and recovery: a new role for progesterone and estrogen?.
AUTHOR: Stein D G
CORPORATE SOURCE: Emory University, Depts of Psychology, Emergency Medicine and Neurology, 30322, Atlanta, GA, USA.
SOURCE: Trends in neurosciences, (2001 Jul) Vol. 24, No. 7, pp. 386-91. Ref: 72
Journal code: 7808616. ISSN: 0166-2236.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 10 Sep 2001
Last Updated on STN: 10 Sep 2001
Entered Medline: 6 Sep 2001

AB Estrogen and progesterone, long considered for their roles as primary hormones in reproductive and maternal behavior, are now being studied as neuroprotective and neuroregenerative agents in stroke and traumatic brain injuries. Collectively, the hormones reduce the consequences of the injury cascade by enhancing anti-oxidant mechanisms, reducing excitotoxicity (altering glutamate receptor activity, reducing immune inflammation, providing neurotrophic support, stimulating axonal remyelinization), and enhancing synaptogenesis and dendritic arborization. Estrogen seems more effective as a prophylactic treatment in females at risk for cardiac and ischemic brain injury, whereas progesterone appears to be more helpful in the post-injury treatment of both male and female subjects with acute traumatic brain damage. However, a recent clinical trial with estradiol replacement therapy in elderly women that have a history of cerebrovascular disease, showed that this hormone was unable to protect against reoccurrence of ischemia or to reduce the incidence of mortality compared to a placebo.

L3 ANSWER 9 OF 42 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:232799 BIOSIS
DOCUMENT NUMBER: PREV200200232799
TITLE: Neuroprotection by NMDA receptor antagonists in a variety of neuropathologies.
AUTHOR(S): Palmer, Gene C. [Reprint author]
CORPORATE SOURCE: Neuroscience Advisory, No. 6 Midgley Lane, Worcester, MA, 01604-3563, USA
eugene.palmer@earthlink.net
SOURCE: Current Drug Targets, (September, 2001) Vol. 2, No. 3, pp. 241-271. print.
ISSN: 1389-4501.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002

L3 ANSWER 10 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:102481 CAPLUS
DOCUMENT NUMBER: 134:293947
TITLE: Serine proteases and brain damage - contribution of the urokinase-plasminogen activator system
AUTHOR(S): Schwab, Jan M.; Meyermann, Richard; Schlüesener, Hermann J.
CORPORATE SOURCE: Institute of Brain Research, University of Tuebingen, Medical School, Tuebingen, FRG-72076, Germany
SOURCE: Trends in Neurosciences (2001), 24(1), 8-9
CODEN: TNSCDR; ISSN: 0166-2236
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A polemic with M.B. Gingrich and S.F. Traynelis (ibid. 2000, 23:399-407) is given. They discussed the role of Ser proteases in neuropathol. of stroke and traumatic brain injury.
In addition to the mechanisms of Ser protease activity described, the authors considered the importance of the urokinase-plasminogen activator system in nervous system pathophysiol.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L3 ANSWER 11 OF 42 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2001104496 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11186229
TITLE: Estrogen-related gender difference in survival rate and cortical blood flow after impact-acceleration head injury in rats.
AUTHOR: Roof R L; Hall E D
CORPORATE SOURCE: Neuroscience Therapeutics, Pfizer Global Research and Development, Ann Arbor Laboratories, Michigan 48105, USA.. robin.roof@pfizer.com
SOURCE: Journal of neurotrauma, (2000 Dec) Vol. 17, No. 12, pp. 1155-69.
Journal code: 8811626. ISSN: 0897-7151.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 8 Feb 2001

AB While a number of laboratories have begun to examine gender differences in outcome following experimental stroke, little is known about the relative response of male and female brains to traumatic injury. In the following series of experiments, we used the Marmarou impact-acceleration head injury model (with a 500-g, 1.5-m weight drop) to compare the pathophysiological responses of male and female rats to closed-head injury. Cortical blood flow (CBF; laser-doppler flowmetry), mean arterial blood pressure (MAP), blood gas levels, blood pH, and body temperature were measured preinjury and at regular intervals postinjury. Acute survival was assessed 1 h after injury. The role of estrogen in the observed gender differences was assessed by examining these physiological measures after injury in ovariectomized females, with or without 17beta-estradiol replacement, and in intact males, with or without exogenous 17beta-estradiol administration. In the first experiment, significantly more females (100%) survived the acute injury period (60 min) after injury than did males (72%). Survival appeared related to the magnitude and persistence of the posttraumatic drop in MAP. In a second experiment, females showed a less dramatic reduction in and better recovery of CBF than males. The gender difference in CBF was paralleled to some degree by differences in the pattern of MAP changes after injury. Differences in body weight, blood gas levels, or blood pH did not account for the gender difference in CBF. Postinjury CBF was higher in female and male rats given 2 weeks of daily 17beta-estradiol injections prior to injury compared to those given the vehicle only. However, 17beta-estradiol administration did not alter MAP, suggesting that the gender difference in CBF was not strictly due to MAP changes. Our findings suggest that estrogen plays a role in maintaining adequate cerebral perfusion in the acute period following closed-head injury. This protective mechanism may underlie the gender difference in acute survival observed in this study, and may help explain observations of better outcome in females than in males after brain injury. We conclude that CBF preservation is one mechanism by which estrogen is neuroprotective following traumatic brain injury. We hypothesize, based upon known effects of estrogen, that the beneficial microvascular effects of estrogen most likely involve a combination of endothelial nitric oxide synthase induction and an antioxidant effect.

L3 ANSWER 12 OF 42 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000348034 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10888932
TITLE: Induction of activin A is essential for the neuroprotective action of basic fibroblast growth factor in vivo.

AUTHOR: Tretter Y P; Hertel M; Munz B; ten Bruggencate G; Werner S; Alzheimer C
CORPORATE SOURCE: Department of Physiology, University of Munich, Pettenkoferstr.12, D-80336 Munchen, Germany.
SOURCE: Nature medicine, (2000 Jul) Vol. 6, No. 7, pp. 812-5.
Journal code: 9502015. ISSN: 1078-8956.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 11 Aug 2000
Last Updated on STN: 11 Aug 2000
Entered Medline: 31 Jul 2000

AB Exogenous application of neurotrophic growth factors has emerged as a new and particularly promising approach not only to promote functional recovery after acute brain injury but also to protect neurons against the immediate effect of the injury. Among the various growth factors and cytokines studied so far, the neuroprotective and neurotrophic profile of basic fibroblast growth factor (bFGF) is the best documented. Using an animal model of acute excitotoxic brain injury, we report here that the neuroprotective action of bFGF, which is now being tested in stroke patients, depends on the induction of activin A, a member of the transforming growth factor-beta superfamily. Our evidence for this previously unknown mechanism of action of bFGF is that bFGF strongly enhanced lesion-associated induction of activin A; in the presence of the activin-neutralizing protein follistatin, bFGF was no longer capable of rescuing neurons from excitotoxic death; and recombinant activin A exerted a neuroprotective effect by itself. Our data indicate that the development of substances influencing activin expression or receptor binding should offer new ways to fight neuronal loss in ischemic and traumatic brain injury.

L3 ANSWER 13 OF 42 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000388239 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10907387
TITLE: Methylphenidate: its pharmacology and uses.
AUTHOR: Challman T D; Lipsky J J
CORPORATE SOURCE: Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN 55905, USA.
SOURCE: Mayo Clinic proceedings. Mayo Clinic, (2000 Jul) Vol. 75, No. 7, pp. 711-21. Ref: 186
Journal code: 0405543. ISSN: 0025-6196.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 18 Aug 2000
Last Updated on STN: 18 Aug 2000
Entered Medline: 9 Aug 2000

AB Methylphenidate is a commonly used medication in the United States. This central nervous system stimulant has a mechanism of action distinct from that of amphetamine. The Food and Drug Administration has approved methylphenidate for the treatment of attention-deficit/hyperactivity disorder and narcolepsy. Treatment with methylphenidate has been advocated in patients with traumatic brain injury and stroke, cancer patients, and those with human immunodeficiency virus infection. Placebo-controlled trials have documented its efficacy as an adjunctive agent in the treatment of depression and pain. This article reviews the current

understanding of the mechanism of action and efficacy of methylphenidate in various clinical conditions.

L3 ANSWER 14 OF 42 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2000265389 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10807109
TITLE: Ginkgo biloba extract: mechanisms and clinical indications.
AUTHOR: Diamond B J; Shiflett S C; Feiwel N; Matheis R J; Noskin O; Richards J A; Schoenberger N E
CORPORATE SOURCE: Department of Research, Center for Research in Complementary and Alternative Medicine, Kessler Medical Rehabilitation Research and Education Corporation, West Orange, NJ 07052, USA.
CONTRACT NUMBER: U24HD32994 (NICHD)
SOURCE: Archives of physical medicine and rehabilitation, (2000 May) Vol. 81, No. 5, pp. 668-78. Ref: 120
Journal code: 2985158R. ISSN: 0003-9993.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 25 May 2000
Last Updated on STN: 25 May 2000
Entered Medline: 18 May 2000

AB OBJECTIVE: Ginkgo biloba may have a role in treating impairments in memory, cognitive speed, activities of daily living (ADL), edema, inflammation, and free-radical toxicity associated with traumatic brain injury (TBI), Alzheimer's dementia, stroke, vasoocclusive disorders, and aging. The purpose of this review is to provide a synthesis of the mechanisms of action, clinical indications, and safety of Ginkgo biloba extract. DATA SOURCES: Empirical studies, reviews, chapters, and conference proceedings were identified in the following databases: Medline, the Research Council for Complementary Medicine based on the British Library database, and Psychlnfo. Ginkgo biloba, EGb 761, Tanakan, Tebonin, Rokan, and LI 1370 were the principal index terms. STUDY SELECTION AND DATA EXTRACTION: Controlled clinical studies with both positive and negative findings are included, in addition to animals studies illustrating mechanisms of activity. DATA SYNTHESIS: Ginkgo has shown activity centrally and peripherally, affecting electrochemical, physiologic, neurologic, and vascular systems in animals and humans with few adverse side effects or drug interactions. Ginkgo shows promise in patients with dementia, normal aging, and cerebrovascular-related disorders. Clinical indications include memory, information processing, and ADL. CONCLUSIONS: Ginkgo shows promise in treating some of the neurologic sequelae associated with Alzheimer's disease, TBI, stroke, normal aging, edema, tinnitus, and macular degeneration. Mechanisms of action may include antioxidant, neurotransmitter/receptor modulatory, and antiplatelet activating factor properties. While safe, caution is advised when recommending ginkgo to patients taking anticoagulants. Future studies should examine dose effects, component activity, mechanisms, and clinical applications.

L3 ANSWER 15 OF 42 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2001019327 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10872746
TITLE: Tin-mesoporphyrin, a potent heme oxygenase inhibitor, for treatment of intracerebral hemorrhage: in vivo and in vitro studies.
AUTHOR: Wagner K R; Hua Y; de Courten-Myers G M; Broderick J P;

Nishimura R N; Lu S Y; Dwyer B E
CORPORATE SOURCE: Department of Neurology, University of Cincinnati College of Medicine, Ohio 45267, USA.. wagnerkr@email.uc.edu
CONTRACT NUMBER: NS-30652 (NINDS)
SOURCE: Cellular and molecular biology (Noisy-le-Grand, France), (2000 May) Vol. 46, No. 3, pp. 597-608.
Journal code: 9216789. ISSN: 0145-5680.
PUB. COUNTRY: France
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200011
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 7 Nov 2000

AB Spontaneous intracerebral hemorrhage (ICH) is the stroke subtype with highest mortality and morbidity. ICH can also occur following traumatic brain injury and thrombolysis for ischemic stroke and myocardial infarction. Development of ICH-induced hemispheric edema can elevate intracranial pressure and cause death. In survivors, edema-related white matter injury can lead to life-long neurological deficits. At present, there are no scientifically proven treatments for ICH. Heme oxygenase products, particularly iron and bilirubin, can be toxic to cells. In cerebral ischemia models, metalloporphyrins that are potent heme oxygenase inhibitors, reduce edema and infarct size. Tin-mesoporphyrin (SnMP) is a neuroprotectant that has also been used clinically to treat hyperbilirubinemia. Presently, we tested the hypothesis that SnMP treatment would reduce edema development following experimental ICH. We produced hematomas in pentobarbital-anesthetized pigs (9-11 kg) by infusing autologous blood into the frontal white matter. To maximize tissue concentrations, SnMP (87.5 microM in DMSO) or DMSO (vehicle controls) was included in the infused blood. Pig brains were frozen in situ at 24 hrs. following ICH and hematoma and edema volumes were determined on coronal sections by computer-assisted image analysis. We also examined the effects of SnMP in vitro on ferritin iron release, the formation of iron-induced thiobarbituric acid reactive substances (TBARS) and initial clot formation and hemolysis. SnMP treatment significantly reduced intracerebral mass following ICH. This was due to significant decreases in hematoma (0.68+/-0.08 vs. 1.39+/-0.30 cc, vehicle controls $p<0.025$) and edema volumes (edema = 1. 16+/-0.33 vs. 1.77+/-0.31 cc, $p<0.05$). In vitro, SnMP did not stabilize ferritin iron against reductive release nor did it decrease iron-induced TBARS formation in brain homogenates. SnMP or DMSO added to pig blood did not alter clot weights. In conclusion, SnMP reduced intracerebral mass in an ICH model by decreasing both hematoma and edema volumes SnMP's mechanism of action is presently unknown but may involve its potent inhibition of heme oxygenase activity. SnMP's effect appears unrelated to ferritin iron release, antioxidant activity or initial clot formation. Since SnMP treatment could be brain protective following ICH, further investigations into neurological and neuropathological outcomes and as well as into its mechanism of action are warranted.

L3 ANSWER 16 OF 42 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 2000290654 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10833057
TITLE: Gender differences in acute CNS trauma and stroke : neuroprotective effects of estrogen and progesterone.
AUTHOR: Roof R L; Hall E D
CORPORATE SOURCE: Neuroscience Therapeutics, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert, Ann Arbor, Michigan 48105, USA.. robin.roof@wl.com

SOURCE: Journal of neurotrauma, (2000 May) Vol. 17, No. 5, pp. 367-88. Ref: 171
Journal code: 8811626. ISSN: 0897-7151.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 11 Aug 2000
Last Updated on STN: 11 Aug 2000
Entered Medline: 31 Jul 2000

AB Increasing evidence has demonstrated striking sex differences in the pathophysiology of and outcome after acute neurological injury. Lesser susceptibility to postischemic and posttraumatic brain injury in females has been observed in experimental models. Additional evidence suggests this sex difference extends to humans as well. The greater neuroprotection afforded to females is likely due to the effects of circulating estrogens and progestins. In fact, exogenous administration of both hormones has been shown to improve outcome after cerebral ischemia and traumatic brain injury in experimental models. The neuroprotection provided by periinjury administration of these hormones extends to males as well. The mechanisms by which estrogen and progesterone provide such neuroprotection are likely multifactorial, and probably depend on the type and severity of injury as well as the type and concentration of hormone present. Both genomic and nongenomic mechanisms may be involved. Estrogen's putative effects include preservation of autoregulatory function, an antioxidant effect, reduction of A beta production and neurotoxicity, reduced excitotoxicity, increased expression of the antiapoptotic factor bcl-2, and activation of mitogen activated protein kinase pathways. It is hypothesized that several of these neuroprotective mechanisms can be linked back to estrogen's ability to act as a potent chemical (i.e., electron-donating) antioxidant. Progesterone, on the other hand, has a membrane stabilizing effect that also serves to reduce the damage caused by lipid peroxidation. In addition, it may also provide neuroprotection by suppressing neuronal hyperexcitability. The following review will discuss experimental and clinical evidence for sex differences in outcome after acute brain trauma and stroke, review the evidence implicating estrogens and progestins as mediators of this neuroprotection following acute neurological injury, and finally, address the specific mechanisms by which these hormones may protect the brain following acute neurological injury.

L3 ANSWER 17 OF 42 EMBASE DUPLICATE 11
ACCESSION NUMBER: 2000356161 EMBASE
TITLE: Dexanabinol (HU-211): A nonpsychotropic cannabinoid with neuroprotective properties.
AUTHOR: Shohami E.; Mechoulam R.
CORPORATE SOURCE: Prof. E. Shohami, Department of Pharmacology, Hebrew University, School of Pharmacy, Jerusalem 91120, Israel. esty@cc.huji.ac.il
SOURCE: Drug Development Research, (2000) Vol. 50, No. 3-4, pp. 211-215.
Refs: 34
ISSN: 0272-4391 CODEN: DDREDK
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 037 Drug Literature Index
039 Pharmacy
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 16 Nov 2000
Last Updated on STN: 16 Nov 2000

AB The synthetic cannabinoid (+)-(6aS,10aS)-11-hydroxy-Δ-8-tetrahydrocannabinol 1',1'-dimethylheptyl (dexanabinol, HU-211)is inactive as a cannabimimetic, but exhibits pharmacological properties characteristic of an N-methyl-D-aspartate (NMDA)-receptor antagonist. It blocks NMDA-receptors stereospecifically by interacting with a site close to, but distinct from, that of uncompetitive NMDA-receptor antagonists and from the recognition sites of glutamate, glycine, and polyamines. HU-211 inhibits the synthesis of tumor necrosis factor alpha (TNFα) and possesses antioxidant properties. HU-211 blocked NMDA-induced (45)Ca uptake by primary neuronal cultures of rat forebrain and protected the same neuronal cultures against NMDA and glutamate neurotoxicity. Moreover, HU-211 effectively scavenged peroxy radicals in vitro and protected cultured neurons from the toxic effects of reactive oxygen species (ROS). In addition, HU-211 markedly suppressed in vitro TNFα production and nitric oxide (NO) generation (by >90%) by both murine peritoneal macrophages and rat alveolar macrophage cell line exposed to lipopolysaccharide (LPS). Since glutamate, ROS and TNFα are implicated in the pathophysiology of various acute conditions, the promising results showing neuroprotection by HU-211, acting via multiple mechanisms, led to a series of studies in which the drug was given to experimental animals. In the present review we discuss results from experiments describing the potential use of HU-211 as a neuroprotective agent in models of traumatic brain injury, stroke, optic nerve injury, pneumacocal meningitis, sepsis, and soman toxicity. In addition, HU-211 was introduced into clinical trials for traumatic brain injury and the successful results of two phases of clinical trials in head injured patients are also shown. (C) 2000 Wiley-Liss, Inc.

L3 ANSWER 18 OF 42 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 2001098289 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11099719
TITLE: Comparison of serum S-100 protein levels following stroke and traumatic brain injury.
AUTHOR: Elting J W; de Jager A E; Teelken A W; Schaaf M J; Maurits N M; van der Naalt J; Sibinga C T; Sulter G A; De Keyser J
CORPORATE SOURCE: Department of Neurology, University Hospital Groningen, Hanzenplein 1, P.O. Box 30.001, 9700RB, Groningen, The Netherlands.. j.w.j.elting@neuro.azg.nl
SOURCE: Journal of the neurological sciences, (2000 Dec 1) Vol. 181, No. 1-2, pp. 104-10.
Journal code: 0375403. ISSN: 0022-510X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 22 Mar 2001
Last Updated on STN: 22 Mar 2001
Entered Medline: 1 Feb 2001

AB Temporal changes in serum S-100 protein levels were compared between patients with ischemic stroke, transient ischemic attack (TIA) and traumatic brain injury (TBI). In addition, S-100 levels were correlated with clinical severity and outcome. Measurements were done with a LIA-mat((R)) Sangtec((R)) 100 using an automated immunoluminometric assay. Serum S-100 was measured in 21 stroke patients, 18 TIA patients and ten TBI patients on days 1 (0-24 h), 2, 3, 4, 5 or 6 and 8 or 9. In a control group of 28 healthy volunteers one measurement was done. For the stroke and TIA patients, National Institutes of Health

Stroke Scale (NIHSS) scores were obtained on admission and on day 10. For the TBI patients, Glasgow Coma Scale (GCS) scores were obtained on admission and Glasgow Outcome Scale (GOS) scores were obtained after 6 months. Changes in serum S-100 levels over the first 3 days were significantly different between stroke and TBI patients (P=0.014) and between stroke and TIA patients (P=0.006). Peak concentrations of S-100 were most often observed on day 3 or 4 after stroke and on day 1 or 2 after TBI. In the stroke patients individual S-100 peak levels correlated well with the NIHSS score on admission (r=0.58 P=0.014) and the change in NIHSS score between day 10 and day 1 (r=0.65, P=0. 005). In the TBI patients a good correlation between individual peak levels of S-100 and the GCS score on admission (r=-0.81, P=0.010) and the GOS score 6 months after the trauma was found (r=-0.87, P=0. 004). We conclude that there is a significant difference in temporal changes of S-100 levels between ischemic stroke and TBI patients. This suggests different pathophysiological mechanisms. The results of this study further confirm that peak levels of serum S-100 correlate with neurological deficit resulting from either stroke or TBI

L3 ANSWER 19 OF 42 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2001:106584 BIOSIS
DOCUMENT NUMBER: PREV200100106584
TITLE: Endothelin-1 is increased in cerebrospinal fluid following traumatic brain injury in children.
AUTHOR(S): Ruppel, R. A. [Reprint author]; Kochanek, P. M.; Adelson, P. D.; Bell, M. J.; Clark, R. S.; Janesko, K. L.; Darnley, A. S.; Berry, S. G.; Jenkins, L. W.; Marion, D. W.
CORPORATE SOURCE: Univ. of Pittsburgh School of Med., and Children's Hospital, Pittsburgh, PA, USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-494.12. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 04-09, 2000. Society for Neuroscience.
ISSN: 0190-5295.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Feb 2001
Last Updated on STN: 15 Feb 2002

AB Cerebral ischemia is often observed early after severe traumatic brain injury (TBI) in infants and children and is associated with poor outcome. The mechanisms underlying the development of cerebral ischemia after TBI remain to be defined. Endothelin-1 (ET-1) is a potent vasoconstrictor peptide that may mediate cerebral ischemia after TBI. ET-1 has been implicated in the ischemia seen in subarachnoid hemorrhage (SAH), stroke, and experimental TBI1. Recent studies have shown increases in ET-1 in cerebrospinal fluid (CSF) from adults with vasospasm after SAH2. The role of ET-1 after TBI in infants and children is unclear. We hypothesized that ET-1 would be increased in the CSF of children with severe TBI, and would peak early after injury. ET-1 concentration was measured (RIA, lower limit of detection = 20 pg/ml) in 87 ventricular CSF samples from 24 infants and children during the initial week after severe TBI. Lumbar CSF samples (n=9) were also analyzed from age-appropriate controls. Standard ICP-directed neurointensive care was used in all patients. Demographics (age, initial GCS, mechanism of injury, and outcome) were recorded for all patients. Data (median, 25th-75th %ile) were analyzed using Mann-Whitney Rank Sum test. Children with severe TBI (ages 0.2 - 13 yr)

presented with a median GCS score of 6. Twenty-one of the 24 children survived. ET-1 concentration was markedly increased in TBI patients (33.5 pg/ml (26.5-50.7)) vs controls (undetectable in all samples, p < 0.001). ET-1 concentration peaked during the initial 24 h after injury. Peak ET-1 concentrations ranged from 24.8-85.6 pg/ml. CSF ET-1 is increased after severe TBI in children and peaks early after injury. We speculate that ET-1 may play a role in the development of early posttraumatic ischemia and may represent a potential therapeutic target.

L3 ANSWER 20 OF 42 EMBASE

ACCESSION NUMBER: 1999381689 EMBASE
TITLE: Caspases: A drug discovery perspective.
AUTHOR: Wang K.K.W.
CORPORATE SOURCE: K.K.W. Wang, Dept. of Neuroscience Therapeutics, Parke-Davis Pharmaceutical Research, 2800 Plymouth Road, Ann Arbor, MI 48105, United States. kevin.wang@wl.com
SOURCE: Current Opinion in Drug Discovery and Development, (1999) Vol. 2, No. 5, pp. 519-527.
Refs: 74
ISSN: 1367-6733 CODEN: CODDFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Dec 1999
Last Updated on STN: 2 Dec 1999

AB Recent advances in the elucidation of the biochemical machinery of apoptosis have allowed us to appreciate the significance of unscheduled apoptosis in a wide range of human diseases and disorders, such as ischemic stroke, traumatic brain injury. Alzheimer's disease, drug-induced liver injury and cardiac ischemia. One of the most exciting advances in this area has been the discovery that a family of intracellular cysteine proteinases (caspases) plays a central role in the apoptosis cascade. Various caspase inhibitors (peptide or protein) have demonstrated abilities to strongly suppress unscheduled apoptotic cell death both in vitro and in vivo. Thus, there is potential to exploit the therapeutic values of caspase inhibition.

=> dis ibib abs l3 21-30
YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' - CONTINUE? (Y)/N:y

L3 ANSWER 21 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1999424129 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10494342
TITLE: Neuroprotective strategies in nature--novel clues for the treatment of stroke and trauma.
AUTHOR: Frerichs K U
CORPORATE SOURCE: Division of Neurosurgery, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.
SOURCE: Acta neurochirurgica. Supplement, (1999) Vol. 73, pp. 57-61.
Journal code: 100962752. ISSN: 0065-1419.
PUB. COUNTRY: Austria
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 1 Nov 1999
Last Updated on STN: 1 Nov 1999
Entered Medline: 20 Oct 1999

AB A myriad of mediators and mechanisms have been implicated as participants in the propagation of damage following stroke and traumatic brain injury. Effective neuroprotection for these conditions, however, remains elusive at the clinical level. Adaptive strategies of animal species that naturally endure severe reductions in nutrient perfusion to the brain may reveal new mechanisms of homeostatic control and tolerance with potential clinical usefulness. A variety of species appear to qualify as models of tolerance, including those that are anoxia tolerant and species capable of hibernation. Mammalian hibernation represents a state in which global physiologic functions are virtually arrested and delivery of glucose and oxygen is minimal, yet homeostatic control is maintained. The profound reduction of cerebral perfusion in hibernation would lead to rapid autolysis of brain tissue in an unprotected state, but has no adverse effects on hibernators and brain damage does not occur. In fact, even hippocampal slices from hibernating ground squirrels and cerebellar slices from anoxia-tolerant turtles show increased tolerance to a superimposed insult of aglycemia and hypoxia. Surprisingly, the cellular mechanisms and signals that trigger and maintain these adaptations remain unknown. Main targets of current investigations are the regulation of the controlled metabolic suppression in hibernation and the mechanisms of preservation of cell structure and membrane functions and integrity despite reduced energy supplies. The possibility of induction of a similar tolerant state in humans by activation of natural mechanisms of reversible cellular arrest employed by hibernators and other tolerant states would have potentially far-reaching clinical implications. This includes prevention of secondary brain damage following brain trauma and ischemia as well as induction of a state of neuroprotection under conditions of anticipated reduction in cerebral perfusion pressure, such as arterial vasospasm after subarachnoid hemorrhage, or during surgical procedures that require temporary circulatory arrest. Induction of a resistant state could also provide additional time until specialized treatment to re-open occluded blood vessels in stroke patients could be administered.

L3 ANSWER 22 OF 42 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 1998132243 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9472901
TITLE: Combating hyperthermia in acute stroke: a significant clinical concern.
AUTHOR: Ginsberg M D; Busto R
CORPORATE SOURCE: Cerebral Vascular Disease Research Center, Department of Neurology, University of Miami School of Medicine, Fla 33101, USA.. mdginsberg@stroke.med.miami.edu
CONTRACT NUMBER: NS 05820 (NINDS)
NS 30291 (NINDS)
SOURCE: Stroke; a journal of cerebral circulation, (1998 Feb) Vol. 29, No. 2, pp. 529-34. Ref: 60
Journal code: 0235266. ISSN: 0039-2499.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 6 Mar 1998
Last Updated on STN: 15 Feb 2003

Entered Medline: 26 Feb 1998

AB BACKGROUND: Moderate elevations of brain temperature, when present during or after ischemia or trauma, may markedly worsen the resulting injury. We review these provocative findings, which form the rationale for our recommendation that physicians treating acute cerebral ischemia or traumatic brain injury diligently monitor their patients for incipient fever and take prompt measures to maintain core-body temperature at normothermic levels. SUMMARY OF REVIEW: In standardized models of transient forebrain ischemia, intraischemic brain temperature elevations to 39 degrees C enhance and accelerate severe neuropathological alterations in vulnerable brain regions and induce damage to structures not ordinarily affected. Conversely, the blunting of even mild spontaneous postischemic hyperthermia confers neuroprotection. Mild hyperthermia is also deleterious in focal ischemia, particularly in reversible vascular occlusion. The action of otherwise neuroprotective drugs in ischemia may be nullified by mild hyperthermia. Even when delayed by 24 hours after an acute insult, moderate hyperthermia can still worsen the pathological and neurobehavioral outcome. Hyperthermia acts through several mechanisms to worsen cerebral ischemia. These include (1) enhanced release of neurotransmitters; (2) exaggerated oxygen radical production; (3) more extensive blood-brain barrier breakdown; (4) increased numbers of potentially damaging ischemic depolarizations in the focal ischemic penumbra; (5) impaired recovery of energy metabolism and enhanced inhibition of protein kinases; and (6) worsening of cytoskeletal proteolysis. Recent studies demonstrate the feasibility of direct brain temperature monitoring in patients with traumatic and ischemic injury. Moderate to severe brain temperature elevations, exceeding core-body temperature, may occur in the injured brain. Cerebral hyperthermia also occurs during rewarming after hypothermic cardiopulmonary bypass procedures. Several studies have now shown that elevated temperature is associated with poor outcome in patients with acute stroke. Finally, recent clinical trials in severe closed head injury have shown a beneficial effect of moderate therapeutic hypothermia. CONCLUSIONS: The acutely ischemic or traumatized brain is inordinately susceptible to the damaging influence of even modest brain temperature elevations. While controlled clinical investigations will be required to establish the therapeutic efficacy and safety of frank hypothermia in patients with acute stroke, the available evidence is sufficiently compelling to justify the recommendation, at this time, that fever be combatted assiduously in acute stroke and trauma patients, even if "minor" in degree and even when delayed in onset. We suggest that body temperature be maintained in a safe normothermic range (eg, 36.7 degrees C to 37.0 degrees C [98.0 degrees F to 98.6 degrees F]) for at least the first several days after acute stroke or head injury.

L3 ANSWER 23 OF 42 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 1999212796 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10197047
TITLE: Therapeutic approaches to the treatment of neuroinflammatory diseases.
AUTHOR: Hays S J
CORPORATE SOURCE: Parke-Davis Pharmaceutical Research, Ann Arbor, MI 48105, USA.
SOURCE: Current pharmaceutical design, (1998 Aug) Vol. 4, No. 4, pp. 335-48. Ref: 112
Journal code: 9602487. ISSN: 1381-6128.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 25 May 1999
Last Updated on STN: 25 May 1999

Entered Medline: 10 May 1999

AB Microglia cells are present in the central nervous system and respond quickly to pathogenic stimuli in order to protect the brain. When these immunological responses activate inappropriately or are prolonged, they can contribute to the neuronal damage observed in many neurodegenerative diseases. A variety of immune system modulators including complement proteins, inflammatory cytokines such IL-1 alpha, IL-1 beta, IL-3, IL-6, TNF-alpha, and S100 beta, colony-stimulating factor-1, coagulation proteins and matrix metalloproteases are made by both microglia and astrocytes. Additionally astrocytes, the predominant glial component of the brain, express cell-adhesion molecules, cytokine receptors and induce nitric oxide synthease. The pathophysiology of Alzheimer's disease, stroke, traumatic brain injury, and multiple sclerosis suggest that a large portion of the irreversible damage observed can be attributed to a neuroinflammatory mechanism. The immunomodulators of these diseases are reviewed and new agents within specific molecular mechanisms are presented and discussed.

L3 ANSWER 24 OF 42 MEDLINE on STN DUPLICATE 15

ACCESSION NUMBER: 1998400139 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9730688
TITLE: Role of the brain in interleukin-6 modulation.
AUTHOR: Terreni L; De Simoni M G
CORPORATE SOURCE: Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy.
SOURCE: Neuroimmunomodulation, (1998 May-Aug) Vol. 5, No. 3-4, pp. 214-9. Ref: 72
Journal code: 9422763. ISSN: 1021-7401.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 6 Jan 1999
Entered Medline: 3 Nov 1998

AB High levels of interleukin 6 (IL-6) have been found in the brain tissue or cerebrospinal fluid (CSF) in several CNS disorders including Alzheimer's disease, AIDS dementia complex, multiple sclerois, stroke, Parkinson's disease, traumatic brain injuries , brain tumors and CNS infections. In these diseases, IL-6 is also found in blood showing that CNS conditions can elicit a peripheral immune response. A direct secretion of IL-6 from brain to blood has been shown to be a major mechanism by which the brain activates peripheral metabolic, endocrine and immune responses. However, this communication is not straightforward and other regulatory mechanisms are likely to be there. Several lines of evidence obtained in the laboratory have shown that the brain significantly modulates IL-6 production in the periphery. Evidence will be given that: (i) central inflammatory stimuli efficiently induce peripheral IL-6; (ii) central opioids are effective modulators of peripheral IL-6, and (iii) the sympathetic nervous system represents an inhibitory pathway to peripheral IL-6.

L3 ANSWER 25 OF 42 MEDLINE on STN DUPLICATE 16

ACCESSION NUMBER: 1998445148 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9774164
TITLE: Mossy fibre innervation is not required for the development of kainic acid toxicity in organotypic hippocampal slice cultures.
AUTHOR: Gatherer M; Sundstrom L E
CORPORATE SOURCE: Department of Clinical Neurosciences, Southampton University, Southampton General Hospital, UK.
SOURCE: Neuroscience letters, (1998 Sep 4) Vol. 253, No.

2, pp. 119-22.
Journal code: 7600130. ISSN: 0304-3940.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 18 Jun 1999
Last Updated on STN: 18 Jun 1999
Entered Medline: 4 Jun 1999

AB The glutamate analogue kainic acid (KA) generates convulsions when applied systemically or directly into the brain and produces lesions comparable to those seen in Ammon's horn sclerosis, observed in many patients with temporal lobe epilepsy. The neurotoxic actions of KA in-vivo appear to be mediated by a combination of direct effects on neurons and indirect effects mediated by seizures. Understanding the contribution of both direct and indirect effects of KA towards neuronal cell death is important for elucidating excitotoxic mechanisms, which may represent a common final pathway in a variety of neurodegenerative disorders including stroke, traumatic brain injury and epilepsy. We have investigated the effects of mossy fibre innervation on the development of KA toxicity in organotypic hippocampal slice cultures in order to assess the role of this input pathway on the specific toxicity of KA toward CA3 pyramidal neurones in vitro.

L3 ANSWER 26 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:695035 CAPLUS
DOCUMENT NUMBER: 130:105143
TITLE: Neuroprotective potential of nimodipine, a cerebral calcium antagonist
AUTHOR(S): Heininger, Kurt
CORPORATE SOURCE: Bayer AG, Wuppertal and Department of Neurology, Heinrich Heine University of Dusseldorf, Germany
SOURCE: Calcium Ion Modulators: The New Wave of Psychotropic Drugs, Selected Papers from the Satellite Symposium Calcium Ion Modulators, Tokyo, Oct. 23, 1996 (1998), Meeting Date 1996, 41-56. Editor(s): Inoue, Kazuhide; Watanabe, Yasuo. Harwood: Amsterdam, Neth.
CODEN: 66WJAH
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Cellular calcium (Ca2+) homeostasis and energy production are closely interdependent. Ca2+ions regulate the activity of a variety of rate-limiting enzymes associated with the tricarboxylic acid cycle and respiratory chain. Maintenance of an optimal transmembrane Ca2+ gradient is necessary to ensure that Ca2+ functions correctly - and this is an energy-dependent process. Under normal circumstances the supply of energy according to demand is regulated by Ca2+ transport across the inner mitochondrial membrane. In certain pathol. conditions, however, the same process induces the formation of oxygen radicals which effect the breakdown of mitochondrial function and structure. Energy deprivation has been shown to be part of the cascade of events that contributes to the evolution of severe neurol. disorders such as stroke, head trauma, subarachnoid hemorrhage (SAH), and Alzheimer's disease (AD). It triggers a sequence of processes which include the release of glutamate, Ca2+ ion influx and generation of reactive oxygen species. It is suggested that the acuity and severity of the energy crisis determine the relative importance of these pathogenic steps. Excitotoxicity is the pathogenic principle in the ischemic core. In the surrounding penumbra, voltage-dependent Ca2+ influx will prevail. Oxygen radicals will form in the hypoxic penumbra rather than in the anoxic ischemic core. Nimodipine is a Ca2+ antagonist that inhibits the influx of Ca2+ ions through

voltage-dependent calcium channels and blocks mitochondrial Ca2+ cycling. It exerts neuroprotective effects in a variety of ischemic conditions. Nimodipine has been shown to provide clin. benefit in patients with delayed ischemic deficit secondary to SAH, and in those with age-related cognitive impairment. Promising results have also been obtained in patients with traumatic SAH, traumatic brain injury and stroke. These findings strengthen the concept that a common Ca2+ -mediated pathogenic mechanism underlies each of these conditions. They also establish nimodipine as an important neuroprotective drug.

REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 27 OF 42 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 97464195 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9324016
TITLE: Heterotopic ossification in the setting of neuromuscular blockade.
AUTHOR: Goodman T A; Merkel P A; Perlmutter G; Doyle M K; Krane S M; Polisson R P
CORPORATE SOURCE: Harvard Medical School, Massachusetts General Hospital, Boston 02114, USA.
SOURCE: Arthritis and rheumatism, (1997 Sep) Vol. 40, No. 9, pp. 1619-27.
Journal code: 0370605. ISSN: 0004-3591.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 5 Nov 1997
Last Updated on STN: 29 Jan 1999
Entered Medline: 23 Oct 1997

AB OBJECTIVE: Heterotopic ossification (HO) is a disorder characterized by the formation of new bone in tissue that does not ossify under normal conditions. We report a series of 6 cases in which HO occurred in the setting of adult respiratory distress syndrome (ARDS). We wished to show that HO can occur after neuromuscular blockade and that these cases might provide additional evidence that HO is influenced by neural mechanisms. METHODS: Cases of HO were selected from the consultation services at the Massachusetts General Hospital and the Brigham and Women's Hospital. Affected patients all had ARDS and had been treated with a neuromuscular blocking agent. Patients with a history of stroke, burn, head trauma, spinal cord injury, or joint replacement were excluded from this study. RESULTS: Heterotopic bone appeared around large joints in a pattern identical to that seen in patients with paralysis, traumatic brain injury, severe burns, or trauma. New bone formation was self-limited over a period of 1-2 years. Alkaline phosphatase and technetium bone scan were sensitive ways of detecting early disease and monitoring disease activity. Medical therapies had limited benefit. Surgical excision of mature new bone appeared to be the only definitive therapy. CONCLUSION: Neuromuscular blockade in the setting of ARDS appears to be an important risk factor for the development of HO. The similarity of these cases of HO occurring in patients with brain or spinal cord injury raises the possibility that neural mechanisms may be important in the pathogenesis of this disease. Whether the type of neuromuscular blocking agent and the duration of use are important determinants of disease severity remains to be determined.

L3 ANSWER 28 OF 42 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 97472554 MEDLINE

DOCUMENT NUMBER: PubMed ID: 9331513
TITLE: Behavioral approaches to the functional assessment of NMDA-mediated neural transmission in intact mice.
AUTHOR: Deutsch S I; Rosse R B; Mastropaolo J
CORPORATE SOURCE: Department of Veterans Affairs Medical Center, Washington, DC 20422, USA.
SOURCE: Clinical neuropharmacology, (1997 Oct) Vol. 20, No. 5, pp. 375-84. Ref: 33
Journal code: 7607910. ISSN: 0362-5664.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 9 Jan 1998
Last Updated on STN: 9 Jan 1998
Entered Medline: 2 Dec 1997

AB Altered neurotransmission mediated by L-glutamate at the level of the N-methyl-D-aspartic acid (NMDA) receptor complex has been implicated in the pathophysiologic mechanisms of several major neuropsychiatric disorders. Moreover, strategies for the pharmacologic manipulation of NMDA-mediated neural transmission have been discussed for the treatment of disorders as diverse as schizophrenia, seizures, stroke, and traumatic brain injury, MK-801, an uncompetitive allosteric antagonist of the NMDA receptor complex, was shown to antagonize electrically precipitated seizures in a dose-dependent manner and elicit popping behavior in mice. Changes in the ability of MK-801 to antagonize electrically precipitated seizures or elicit popping behavior caused by stress or pharmacologic manipulations may reflect alterations in the populations of NMDA-associated channels responsible for these behavioral actions (e.g., the number of them in the open configuration or their size, shape, and charge characteristics). We used these paradigms to study the pharmacologic actions of an allosteric glycinergic intervention (i.e., milacemide), inhibitors of the "nitric oxide cascade" (i.e., 7-nitroindazole and methylene blue), and conventional (i.e., haloperidol) and atypical (i.e., clozapine) antipsychotic medications on NMDA-mediated neurotransmission in the intact mouse. Also, marked differences in the ability of MK-801 to elicit popping behavior in inbred mouse strains suggest that they differ in their populations of NMDA receptor complexes responsible for mediating this behavior. This latter observation could lend itself to the identification of specific genetic loci contributing to this behavior. In view of the ability of phencyclidine (PCP) to precipitate a schizophreniform psychosis and the action it shares with MK-801 on NMDA-mediated neurotransmission, the characterization of these genetic loci in mice may inform the search for human loci responsible for the susceptibility to "PCP-psychosis" and schizophrenia.

L3 ANSWER 29 OF 42 MEDLINE on STN
ACCESSION NUMBER: 1999044220 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9826984
TITLE: Traditional pharmacological treatments for spasticity. Part II: General and regional treatments.
AUTHOR: Gracies J M; Nance P; Elovic E; McGuire J; Simpson D M
CORPORATE SOURCE: Department of Neurology, Mount Sinai Medical Center, New York, NY 10029, USA.
SOURCE: Muscle & nerve. Supplement, (1997) Vol. 6, pp. S92-120. Ref: 162
Journal code: 9517433.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 4 Dec 1998

AB Systemic pharmacologic treatments may be indicated in conditions in which the distribution of muscle overactivity is diffuse. Antispastic drugs act in the CNS either by suppression of excitation (glutamate) enhancement of inhibition (GABA, glycine), or a combination of the two. Only four drugs are currently approved by the US FDA as antispactic agents: baclofen, diazepam, dantrolene sodium, and tizanidine. However, there are a number of other drugs available with proven antispastic action. This chapter reviews the pharmacology, physiology of action, dosage, and results from controlled clinical trials on side effects, efficacy, and indications for 21 drugs in several categories. Categories reviewed include agents acting through the GABAergic system (baclofen, benzodiazepines, piracetam, progabide); drugs affecting ion flux (dantrolene sodium, lamotrigine, riluzole; drugs acting on monoamines (tizanidine, clonidine, thymoxamine, beta blockers, and cyproheptadine); drugs acting on excitatory amino acids (orphenadrine citrate); cannabinoids; inhibitory neuromediators; and other miscellaneous agents. The technique, advantages and limitations of intrathecal administration of baclofen, morphine, and midazolam are reviewed. Two consistent limitations appear throughout the controlled studies reviewed: the lack of quantitative and sensitive functional assessment and the lack of comparative trials between different agents. In the majority of trials in which meaningful functional assessment was included, the study drug failed to improve function, even though the antispastic action was significant. Placebo-controlled trials of virtually all major centrally acting antispastic agents have shown that sedation, reduction of global performance, and muscle weakness are frequent side effects. It appears preferable to use centrally acting drugs such as baclofen, tizanidine, and diazepam in spasticity of spinal origin (spinal cord injury and multiple sclerosis), whereas dantrolene sodium, due to its primarily peripheral mechanism of action, may be preferable in spasticity of cerebral origin (stroke and traumatic brain injury) where sensitivity to sedating effects is generally higher. Intrathecal administration of antispastic drugs has been used mainly in cases of muscle overactivity occurring primarily in the lower limbs in nonambulatory, severely disabled patients but new indications may emerge in spasticity of cerebral origin. Intrathecal therapy is an invasive procedure involving long-term implantation of a foreign device, and the potential disadvantages must be weighed against the level of disability in each patient and the resistance to other forms of antispastic therapy. In all forms of treatment of muscle overactivity, one must distinguish between two different goals of therapy: improvement of active function and improvement of hygiene and comfort. The risk of global performance reduction associated with general or regional administration of antispastic drugs may be more acceptable when the primary goal of therapy is hygiene and comfort than when active function is a priority.

L3 ANSWER 30 OF 42 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 1998:98478 BIOSIS
DOCUMENT NUMBER: PREV199800098478
TITLE: Traditional pharmacological treatment for spasticity: Part II. General and regional treatments.
AUTHOR(S): Gracies, Jean-Michel [Reprint author]; Elovic, Elie; McGuire, John; Simpson, David
CORPORATE SOURCE: Dep. Neurol., 1 Gustave L. Levy Place, New York, NY 10029, USA
SOURCE: Muscle and Nerve, (1997) Vol. 0, No. SUPPL. 6, pp. S92-S120. print.

CODEN: MUNEDE. ISSN: 0148-639X.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Feb 1998
Last Updated on STN: 6 Apr 1998

AB Systemic pharmacologic treatments may be indicated in conditions in which the distribution of muscle overactivity is diffuse. Antispastic drugs act in the CNS either by suppression of excitation (glutamate), enhancement of inhibition (GABA, glycine), or a combination of the two. Only four drugs are currently approved by the US FDA as antispastic agents: baclofen, diazepam, dantrolene sodium, and tizanidine. However, there are a number of other drugs available with proven antispastic action. This chapter reviews the pharmacology, physiology of action, dosage, and results from controlled clinical trials on side effects, efficacy, and indications for 21 drugs in several categories. Categories reviewed include agents acting through the GABAergic system (baclofen, benzodiazepines, piracetam, progabide); drugs affecting ion flux (dantrolene sodium, lamotrigine, riluzole); drugs acting on monoamines (tizanidine, clonidine, thymoxamine, beta blockers, and cyproheptadine); drugs acting on excitatory amino acids (orphenadrine citrate); cannabinoids; inhibitory neuromediators; and other miscellaneous agents. The technique, advantages, and limitations of intrathecal administration of baclofen, morphine, and midazolam are reviewed. Two consistent limitations appear throughout the controlled studies reviewed: the lack of quantitative and sensitive functional assessment and the lack of comparative trials between different agents. In the majority of trials in which meaningful functional assessment was included, the study drug failed to improve function, even though the antispastic action was significant. Placebo-controlled trials of virtually all major centrally acting antispastic agents have shown that sedation, reduction of global performance, and muscle weakness are frequent side effects. It appears preferable to use centrally acting drugs such as bactofen, tizanidine, and diazepam in spasticity of spinal origin (spinal cord injury and multiple sclerosis), whereas dantrolene sodium, due to its primarily peripheral mechanism of action, may be preferable in spasticity of cerebral origin (stroke and traumatic brain injury) where sensitivity to sedating effects is generally higher. Intrathecal administration of antispastic drugs has been used mainly in cases of muscle overactivity occurring primarily in the lower limbs in nonambulatory, severely disabled patients, but new indications may emerge in spasticity of cerebral origin. Intrathecal therapy is an invasive procedure involving long-term implantation of a foreign device, and the potential disadvantages must be weighed against the level of disability in each patient and the resistance to other forms of antispastic therapy in all forms of treatment of muscle overactivity, one must distinguish between two different goals of therapy: improvement of active function and improvement of hygiene and comfort. The risk of global performance reduction associated with general or regional administration of antispastic drugs may be more acceptable when the primary goal of therapy is hygiene and comfort than when active function is a priority.

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YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' - CONTINUE?
(Y)/N:y

L3 ANSWER 31 OF 42 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:481887 CAPLUS
DOCUMENT NUMBER: 127:156088
TITLE: Clinical experience with the NMDA ion channel blocker, aptiganel hydrochloride (CERESTAT)
AUTHOR(S): Knapp, Andrew G.; Mathews, Laima I.; Gamzu, Elkan R.

CORPORATE SOURCE: Cambridge NeuroSci., Inc., Cambridge, MA, 02139, USA
SOURCE: Excitatory Amino Acids: Clinical Results with Antagonists (1997), 31-42, 129-152.
Editor(s): Herrling, P. L. Academic: London, UK.
CODEN: 64UIAO
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB Aptiganel hydrochloride (CERESTAT, CNS 1102), is a novel N-methyl-D-aspartate (NMDA) ion channel blocker (Reddy et al., 1994) being developed for the treatment of stroke and severe traumatic brain injury (TBI).
Originally identified in radioligand binding expts., aptiganel is a potent (28 nM) and selective ligand for the ion channel site of the NMDA receptor (Kirk et al., 1994). It exhibits the in vivo pharmacol. expected for compds. with this mechanism of action: the principal effects in animals are signs of central nervous system excitation (increased spontaneous activity, stereotypies) and depression (ataxia, sedation), as well as modest increases in blood pressure in conscious animals. These effects have a rapid onset, indicating that aptiganel enters have a rapid onset, indicating that aptiganel enters the brain readily, a conclusion confirmed by studies with radiolabeled aptiganel. The elimination half-life of the compound is approx. 1 h in nonhuman species. Aptiganel is a potent anticonvulsant and has been shown to be neuroprotective in several in vitro and in vivo models of cerebral ischemia. A review with over 200 refs. When aptiganel HCl is administered following middle cerebral artery occlusion (MCAO) in rats, neurol. improvement and redns. in infarct volume of up to 70% have been reported (Minematsu et al., 1993b). In such animal models of stroke, plasma levels of ≥10 ng ml-1 were associated with neuroprotection. The compound has a favorable safety profile in animals: single-dose, repeated-dose (up to 90 days), and reproductive toxicity studies have been completed. Over 300 volunteers and patients have been exposed to aptiganel HCl in a series of phase I (Muir et al., 1994) and phase II studies (Gamzu, 1995). These studies have demonstrated that aptiganel HCl can be safely given in doses that produce plasma levels and plasma 'areas under the curve' (AUCs) that have been associated with neuroprotection in animal models. In conscious individuals, the principal dose-limiting effects have been central nervous system complaints, including disorientation, confusion, sedation, and nausea. Agitation and hallucinations occur infrequently. Increases in systolic blood pressure and heart rate have also been observed The pharmacokinetics of this compound in man are highly favorable for parenteral administration in an acute-care setting and do not change with prolonged administration. The plasma elimination half-life in man is about 4 h. Continuous i.v. treatment durations of 72 h have been achieved in severe TBI patients; 12 h treatments have been achieved in stroke patients (Fayad et al., 1996). Although not designed to evaluate efficacy, the early studies have shown some nonsignificant beneficial effects. Pivotal efficacy studies in stroke and TBI began in 1996.

L3 ANSWER 32 OF 42 EMBASE
ACCESSION NUMBER: 1996148979 EMBASE
TITLE: Cholinergic control of cerebral blood flow in stroke, trauma and aging.
AUTHOR: Scremin O.U.; Jenden D.J.
CORPORATE SOURCE: O.U. Scremin, Geriatric Res./Education Clin. Ctr., West Los Angeles VA Medical Center, UCLA School of Medicine, Los Angeles, CA 90073, United States
SOURCE: Life Sciences, (26 Apr 1996) Vol. 58, No. 22, pp. 2011-2018.
Refs: 44
ISSN: 0024-3205 CODEN: LIFSAK
COUNTRY: United States

DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 008 Neurology and Neurosurgery
005 General Pathology and Pathological Anatomy
037 Drug Literature Index
030 Clinical and Experimental Pharmacology
029 Clinical and Experimental Biochemistry
020 Gerontology and Geriatrics
002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jun 1996
Last Updated on STN: 24 Jun 1996

AB Enhancing the availability of endogenous acetylcholine by inhibition of cholinesterase with physostigmine, eptastigmine or soman at sub-toxic doses increases cerebral blood flow (CBF) and the response of this variable to changes in PaCO(2). These effects are not correlated with metabolic activation, suggesting that the function of the cholinergic vasodilatation is not merely to supply metabolic substrates. Since choline (Ch) can exchange between blood and the brain extracellular milieu the stage is set for possible feedback interactions between ACh synthesis and CBF. A negative feedback of CBF on ACh synthesis under conditions of a negative arteriovenous (A-V) difference for Ch across cerebral capillaries may contribute to stabilize CBF in ischemia. Eptastigmine and physostigmine significantly improve perfusion in experimental models of focal cerebral ischemia and traumatic brain injury respectively. During the short periods of time in which the A-V difference for Ch across the brain is positive, a positive feedback between cerebral free Ch and CBF may enhance the ability of the brain to recover Ch from the circulation for synthesis of membrane phospholipids. A loss of cholinergic cerebrovascular control may thus impair the survival of all cells within the CNS and contribute to the pathophysiology of dementia. Perhaps the view that the loss of cholinergic cells is the end point of Alzheimer's dementia could be modified to state that a cholinergic deficit may be the starting point of a decline in cerebral phospholipid turnover and cell membrane renewal that could lead to a generalized deterioration of cerebral function.

L3 ANSWER 33 OF 42 MEDLINE on STN DUPLICATE 19
ACCESSION NUMBER: 96412852 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8816098
TITLE: Use of clonidine for treatment of spasticity arising from various forms of brain injury: a case series.
AUTHOR: Dall J T; Harmon R L; Quinn C M
CORPORATE SOURCE: Western Musculoskeletal Associates, Salt Lake City, UT 84124, USA.
SOURCE: Brain injury : [BI], (1996 Jun) Vol. 10, No. 6, pp. 453-8.
Journal code: 8710358. ISSN: 0269-9052.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 6 Nov 1996
Last Updated on STN: 6 Nov 1996
Entered Medline: 18 Oct 1996

AB Spasticity may occurs as a result of different types of brain injury. The experience with six patients, aged 17-73 years, treated with clonidine for spasticity due to brain injuries of various causes is presented. These cases include a patient with traumatic brain injury, three patients with intracranial haemorrhage, a patient with a right basal ganglia stroke 3 years prior to a left subdural haematoma associated with a fall, and a patient with cerebral

palsy. To varying degrees for each patient, clonidine was effective in reducing extremity hypertonicity. A possible mechanism of action is discussed. These case findings suggest clonidine may be useful in the management of spasticity associated with various forms of brain injury, and that formal studies of clonidine for this application appear warranted.

L3 ANSWER 34 OF 42 MEDLINE on STN DUPLICATE 20
ACCESSION NUMBER: 97129440 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8973948
TITLE: Therapeutic neural effects of electrical stimulation.
AUTHOR: Daly J J; Marsolais E B; Mendell L M; Rymer W Z; Stefanovska A; Wolpaw J R; Kantor C
CORPORATE SOURCE: VA Medical Center, Cleveland, OH 44106, USA.
CONTRACT NUMBER: P0I NS14899 (NINDS)
R0I NS16996 (NINDS)
R0I NS32264 (NINDS)
+
SOURCE: IEEE transactions on rehabilitation engineering : a publication of the IEEE Engineering in Medicine and Biology Society, (1996 Dec) Vol. 4, No. 4, pp. 218-30.
Ref: 88
Journal code: 9413994. ISSN: 1063-6528.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 27 Mar 1997
Last Updated on STN: 27 Mar 1997
Entered Medline: 19 Mar 1997

AB The use of a functional neuromuscular stimulation (FNS) device can have therapeutic effects that persist when the device is not in use. Clinicians have reported changes in both voluntary and electrically assisted neuromuscular function and improvements in the condition of soft tissue. Motor recovery has been observed in people with incomplete spinal cord injury, stroke, or traumatic brain injury after the use of motor prostheses. Improvement in voluntary dorsiflexion and overall gait pattern has been reported both in the short term (several hours) and permanently. Electrical stimulation of skin over flexor muscles in the upper limb produced substantial reductions for up to 1 h in the severity of spasticity in brain-injured subjects, as measured by the change in torque generation during ramp-and-hold muscle stretch. There was typically an aggravation of the severity of spasticity when surface stimulation reached intensities sufficient to also excite muscle. Animals were trained to alter the size of the H-reflex to obtain a reward. The plasticity that underlies this operantly conditioned H-reflex change includes changes in the spinal cord itself. Comparable changes appear to occur with acquisition of certain motor skills. Current studies are exploring such changes in humans and animals with spinal cord injuries with the goal of using conditioning methods to assess function after injury and to promote and guide recovery of function. A better understanding of the mechanisms of neural plasticity, achieved through human and animal studies, may help us to design and implement FNS systems that have the potential to produce beneficial changes in the subject's central nervous systems.

L3 ANSWER 35 OF 42 MEDLINE on STN
ACCESSION NUMBER: 96320780 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8734559
TITLE: Diagnosis, physiology, pathology and rehabilitation of

traumatic brain injuries.

AUTHOR: Berker E

CORPORATE SOURCE: Psychology Department, Western Michigan University, Kalamazoo 49008, USA.

SOURCE: The International journal of neuroscience, (1996 Apr) Vol. 85, No. 3-4, pp. 195-220. Ref: 135
Journal code: 0270707. ISSN: 0020-7454.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199610

ENTRY DATE: Entered STN: 22 Oct 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 4 Oct 1996

AB Accumulating clinical and experimental studies continue to elucidate and further define the significance of intra- and extra-cranial factors which determine outcome of traumatic brain injury. These factors include severity of injury, age of the patient, presence or absence of premorbid brain insults, and associated pathophysiological events such as anoxia, respiratory arrest, hemorrage, edema, contrecoup and Wallerian degeneration. Following resolution of acute temporary symptoms, delayed complications include seizures, neurotic and psychotic disorders, earlier onset of stroke, earlier senescence, increased suicide risk, reduced life expectancy, progressive intellectual deterioration and development of symptoms comprising the post-traumatic syndrome. In spite of these diverse initial and later pathological sequelae, the reserve capacities of the brain for establishment of compensatory mechanisms can provide bases for a remarkable degree of spontaneous cerebral reorganization and recovery. The accumulating findings in patients with traumatic brain injuries reflect principles and factors underlying the organization, disorganization and reorganization of human brain function.

L3 ANSWER 36 OF 42 MEDLINE on STN DUPLICATE 21

ACCESSION NUMBER: 96255326 MEDLINE

DOCUMENT NUMBER: PubMed ID: 8689265

TITLE: Neuroprotective properties of calcium-channel blockers.

AUTHOR: Zornow M H; Prough D S

CORPORATE SOURCE: Department of Anesthesiology, University of Texas Medical Branch, Galveston 77555-0591, USA.

SOURCE: New horizons (Baltimore, Md.), (1996 Feb) Vol. 4, No. 1, pp. 107-14. Ref: 58
Journal code: 9416195. ISSN: 1063-7389.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199608

ENTRY DATE: Entered STN: 11 Sep 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 26 Aug 1996

AB Increases in intraneuronal Ca2+ concentration, which accompany cerebral ischemia and traumatic brain injury, initiate a cascade of biochemical events that can eventually result in cell lysis and death. Calcium-channel blockers, in certain experimental models of focal and global ischemia, attenuate the increase in intracellular Ca2+ concentration and thereby ameliorate neurologic damage. Clinical efficacy varies among disease states. After nontraumatic subarachnoid hemorrhage, nimodipine has become a standard of care. Calcium-channel blockers improve outcome, whether given before or after onset of vasospasm. Although the precise mechanism of their

beneficial effect remains unclear (vasodilation vs. attenuation of increases in intracellular Ca2+ concentrations), numerous studies have demonstrated decreased neurologic morbidity. Although there also is suggestive evidence of benefit in human stroke, these results have not been sufficiently impressive to result in the widespread use of these drugs as neuroprotectants. In clinical trials after cardiac arrest, calcium-channel blockers have been ineffective. In clinical traumatic brain injury, data suggest moderate efficacy in younger patients and those with post-traumatic subarachnoid hemorrhage, although overall outcome is not changed. The future role of calcium-channel blockers as neuroprotectants appears bright. Newer classes of compounds, with greater specificity and fewer side effects, may provide greater clinical benefit.

L3 ANSWER 37 OF 42 MEDLINE on STN DUPLICATE 22

ACCESSION NUMBER: 96423926 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8826526
TITLE: Calcium and Free Radicals: Mediators of neurotrophic factor and excitatory transmitter-regulated developmental plasticity and cell death.
AUTHOR: Mattson M P
CORPORATE SOURCE: Sanders-Brown Research Center on Aging, University of Kentucky, Lexington 40536-0230, USA.
SOURCE: Perspectives on developmental neurobiology, (1996) Vol. 3, No. 2, pp. 79-91. Ref: 101
Journal code: 9417971. ISSN: 1064-0517.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 16 Dec 1996

AB An intricate interplay between neurotrophic factor and excitatory transmitter signaling systems exists in both the developing and adult brain. Interactions between these signaling systems appears to be a fundamental mechanism regulating adaptive neuritic pruning and cell death. Accordingly, genetically and environmentally induced imbalances in this regulatory system are implicated in the pathogenesis of a variety of acute (such as stroke and traumatic brain injury) and chronic (such as Alzheimer's and Parkinson's diseases) neurodegenerative disorders. Neurons exhibit both acute and delayed responses to neurotrophic factors and excitatory transmitters; acute responses include rapid structural remodeling of growth cones and synaptic contacts, and delayed responses include induction or suppression of the expression of gene products involved in neuroprotection. Intracellular free Ca2+ and free radicals appear to play key roles as mediators of both acute and delayed responses of neurons to excitatory transmitters and neurotrophic factors. For example, the delayed response to bFGF includes stabilization of Ca2+ homeostasis and induction of antioxidant enzymes; both of these actions of bFGF antagonize the dendrite outgrowth-stabilizing and excitotoxic actions of glutamate. Intricate regulatory interactions exist between glutamate and neurotrophic factor signaling systems so that glutamate can induce the expression of neurotrophic factors and their receptors, and neurotrophic factors modulate the expression of exitatory transmitter receptors. A novel signaling system that can interact with both glutamate and neurotrophic factor systems is that of the beta-amyloid precursor protein, which appears to play important roles in neuronal plasticity and survival. A working model for the regulation of neuronal survival and connectivity is

presented, which considers spatial and temporal constraints on release of, and receptors for, neurotrophic factors and excitatory transmitters.

L3 ANSWER 38 OF 42 MEDLINE on STN DUPLICATE 23
ACCESSION NUMBER: 96158427 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8594209
TITLE: Transgenic mice and knockout mutants in the study of oxidative stress in brain injury.
AUTHOR: Chan P H; Epstein C J; Li Y; Huang T T; Carlson E; Kinouchi H; Yang G; Kamii H; Mikawa S; Kondo T; +
CORPORATE SOURCE: Department of Neurology and Neurosurgery, University of California at San Francisco 94143-0651, USA.
CONTRACT NUMBER: AG-08938 (NIA)
NS-14543 (NINDS)
NS-25372 (NINDS)
SOURCE: Journal of neurotrauma, (1995 Oct) Vol. 12, No. 5, pp. 815-24. Ref: 63
Journal code: 8811626. ISSN: 0897-7151.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199604
ENTRY DATE: Entered STN: 22 Apr 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 9 Apr 1996

AB A rapid increase in the need to explore the molecular basis of cellular function and injury in the central nervous system has led neuroscientists to employ transgenic mouse technology. The successful making of transgenic mice (Tg) overexpressing human CuZn-superoxide dismutase (SOD-1) activity has made it possible to investigate the role of oxygen free radicals in ischemic and traumatic brain injury in a molecular fashion. It has been demonstrated that the 3-fold increase in SOD-1 transgene activity in SOD-1 Tg mice offers protection against cerebral ischemia and reperfusion in two different models of focal cerebral ischemia, as compared to nontransgenic wild-type littermates. Studies involving traumatic brain injury have also demonstrated that acute injuries, including brain edema and blood-brain barrier permeability, are significantly reduced in SOD-1 Tg mice. Furthermore, chronic neurological deficits, such as beam walking, beam balance, and body weight, are significantly improved in these transgenic animals following traumatic brain injury. In addition to the SOD-1 Tg mice being a useful tool for the study of CNS injury, targeted disruption of the mouse gene for mitochondrial manganese SOD (SOD-2) has been successful. These SOD-2 knockout mutant mice, in addition to the recently developed knockout mutants of neuronal nitric oxide synthase (NOS), are believed to offer a unique opportunity to elucidate the oxidative mechanisms in brain injury following stroke and trauma.

L3 ANSWER 39 OF 42 EMBASE
ACCESSION NUMBER: 1995077300 EMBASE
TITLE: Clinical experience with excitatory amino acid antagonist drugs.
AUTHOR: Muir K.W.; Lees K.R.
CORPORATE SOURCE: K.W. Muir, Western Infirmary, Univ. Dept. of Medicine/Therapeutics, Glasgow G11 6NT, United Kingdom
SOURCE: Stroke, (Mar 1995) Vol. 26, No. 3, pp. 503-513.
Refs: 118
ISSN: 0039-2499 CODEN: SJCCA7
COUNTRY: United States

DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 037 Drug Literature Index
038 Adverse Reactions Titles
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Mar 1995
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AB Background. Excitotoxic damage due to excess release of neuronal glutamate is hypothesized to play a pivotal role in the pathogenesis of focal cerebral ischemia. Drugs that antagonize excitatory amino acid function are consistently neuroprotective in preclinical models of stroke, and many are now entering clinical trials. Summary. Antagonists of the N-methyl-D- aspartate (NMDA) receptor are furthest advanced in clinical development for stroke. Both noncompetitive (aptiganel hydrochloride, dextrorphan) and competitive (selfotel, d-CPPene) antagonists have undergone tolerability studies in acute stroke and traumatic brain injury. These agents all cause a similar spectrum of neuropsychological symptoms, and several have important cardiovascular effects. Other modulatory sites on the NMDA receptor complex, notably the polyamine and magnesium ion sites, are also the subject of clinical trials. Glycine site antagonists are in early clinical development. Non-NMDA glutamate receptor antagonists remain in preclinical study. Neuroprotection by agents that block glutamate release in vitro may be due to sodium channel blockade in vivo, but some agents (619C89) exhibit neurological effects similar to NMDA antagonists in stroke. The therapeutic index is unknown for different drugs but may be determined by cardiovascular effects, especially hypotension, which may be detrimental after stroke. Conclusions. Excitatory amino acid antagonists are in advanced development in the treatment of stroke and traumatic brain injury. A similar pattern of side effects is apparent with the majority of agents. However, cardiovascular effects may ultimately define therapeutic index for each drug.

L3 ANSWER 40 OF 42 EMBASE
ACCESSION NUMBER: 1995074455 EMBASE
TITLE: The potential of 21-aminosteroids (Lazaroids) as neuroprotective therapies in CNS injury.
AUTHOR: Smith D.H.; Gennarelli A.; McIntosh T.K.
CORPORATE SOURCE: Dr. D.H. Smith, Division of Neurosurgery, 250 South 33rd Street, Philadelphia, PA 19104-6316, United States
SOURCE: CNS Drugs, (1995) Vol. 3, No. 3, pp. 159-164.
ISSN: 1172-7047 CODEN: CNDREF
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
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Last Updated on STN: 5 Apr 1995

AB Following injury to the CNS, highly reactive free radicals may produce secondary or delayed tissue damage via peroxidation of lipids in cellular membranes. This extensive generation of free radicals appears to overwhelm natural defence mechanisms, dramatically reducing the levels of endogenous antioxidant p compounds. In numerous studies utilising models of CNS injury, treatment with a synthetic antioxidant, the nonglucocorticoid 21-aminosteroid (lazaroid) tirilazad, has been shown to maintain the level of endogenous antioxidants, improve neurological outcome, decrease cell loss, reduce cerebral oedema formation and improve

survival. As a result of these encouraging results, clinical trials have been initiated to evaluate the utility of tirilazad in the treatment of subarachnoid haemorrhage, spinal cord injury, traumatic brain injury and stroke.

L3 ANSWER 41 OF 42 MEDLINE on STN DUPLICATE 24
ACCESSION NUMBER: 92373299 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1506882
TITLE: Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography.
AUTHOR: Bouma G J; Muizelaar J P; Stringer W A; Choi S C; Fatouros P; Young H F
CORPORATE SOURCE: Division of Neurosurgery, Medical College of Virginia, Virginia Commonwealth University, Richmond.
SOURCE: Journal of neurosurgery, (1992 Sep) Vol. 77, No. 3, pp. 360-8.
Journal code: 0253357. ISSN: 0022-3085.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 9 Oct 1992
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Sep 1992

AB The role of cerebral ischemia in the pathophysiology of traumatic brain injury is unclear. Cerebral blood flow (CBF) measurements with 133Xe have thus far revealed ischemia in a substantial number of patients only when performed between 4 and 12 hours postinjury. But these studies cannot be performed sooner after injury, they cannot be done in patients with intracranial hematomas still in place, and they cannot detect focal ischemia. Therefore, the authors performed CBF measurements in 35 comatose head-injured patients using stable xenon-enhanced computerized tomography (CT), simultaneously with the initial CT scan (at a mean (+/- standard error of the mean) interval of 3.1 +/- 2.1 hours after injury). Seven patients with diffuse cerebral swelling had significantly lower flows in all brain regions measured as compared to patients without swelling or with focal contusions; in four of the seven, cerebral ischemia (CBF less than or equal to 18 ml/100 gm.min-1) was present. Acute intracranial hematomas were associated with decreased CBF and regional ischemia in the ipsilateral hemisphere, but did not disproportionately impair brain-stem blood flow. Overall, global or regional ischemia was found in 11 patients (31.4%). There was no correlation between the presence of hypoxia or hypertension before resuscitation and the occurrence of ischemia, neither could ischemia be attributed to low pCO2. Ischemia was significantly associated with early mortality (p less than 0.02), whereas normal or high CBF values were not predictive of favorable short-term outcome. These data support the hypothesis that ischemia is an important secondary injury mechanism after traumatic brain injury, and that trauma may share pathophysiological mechanisms with stroke in a large number of cases; this may have important implications for the use of hyperventilation and antihypertensive drugs in the acute management of severely head-injured patients, and may lead to testing of drugs that are effective or have shown promise in the treatment of ischemic stroke.

L3 ANSWER 42 OF 42 MEDLINE on STN DUPLICATE 25
ACCESSION NUMBER: 90331243 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2376865
TITLE: Characterization of axonal injury produced by controlled cortical impact.
AUTHOR: Lighthall J W; Goshgarian H G; Pinderski C R

CORPORATE SOURCE: Biomedical Science Department, General Motors Research Laboratories, Warren, Michigan.
SOURCE: Journal of neurotrauma, (1990 Summer) Vol. 7, No. 2, pp. 65-76.
Journal code: 8811626. ISSN: 0897-7151.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 12 Oct 1990
Last Updated on STN: 12 Oct 1990
Entered Medline: 5 Sep 1990

AB Axonal injury and behavioral changes were evaluated 3-7 days after traumatic brain injury. Previous research from this laboratory demonstrated that clinical central nervous pathology is produced by dynamic brain compression using a stroke -constrained impactor. We wanted to determine if the technique also would produce diffuse axonal injury after recovery from the procedure. The experiments were performed at Wayne State University School of Medicine using aseptic techniques while assuring analgesic care. Impacts were performed at 4.3 m/sec or 8.0 m/sec, with congruent to 10% compression (2.5 mm). Extensive axonal injury was observed at 3 and 7 days postinjury using both velocity-compression combinations. Regions displaying axonal injury were the subcortical white matter, internal capsule, thalamic relay nuclei, midbrain, pons, and medulla. Axonal injury also was evident in the white matter of the cerebellar folia and the region of the deep cerebellar nuclei. Behavioral assessment showed functional coma lasting up to 36 h following 8.0 m/sec impacts, with impaired movement and control of the extremities over the duration of the postinjury monitoring time. These experiments confirm that the cortical impact model of traumatic brain injury mimics all aspects of traumatic brain injury in humans and can be used to investigate mechanisms of axonal damage and prolonged behavioral suppression.

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